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A Highly *dl*-Stereoselective Pinacolization of Aromatic Aldehydes Mediated by Titanium Trichloride in Dichloromethane

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Abstract: Aromatic aldehydes are stereoselectively coupled to *dl*-hydrobenzoins on treatment with anhydrous $TiCl_3/CH_2Cl_2$ solution at room temperature. The observed stereochemistry is briefly discussed in term of Ti(IV)-bridging control.

The reductive coupling of carbonyl compounds to give pinacols is an important group of carbon-carbon bond forming reactions, which can be accomplished with a variety of one- or two-electron metal reducing agents. Although this reaction has been extensively studied[1,2] very few methods have been so far reported that allow highly stereocontrolled construction of the 1,2-diol unit.

Among the known methods, a highly *dl*-selective pinacolization procedure has been recently reported utilising $NbCl_3$/DME system[3] at -10°C. This reaction occurs *via* an anionic intermediate which acts as a nucleophile towards a second carbonyl group. However, the majority of pinacolic coupling processes involves dimerization of two ketyl radicals and, generally, affords a mixture of *dl* and *meso* diols.[1,4]

In 1973, Mukayama reported[5] that "*$TiCl_3$ does not reduce benzaldehyde in THF at room temperature*" and since then a considerable variety of pinacolization procedures employing stronger reducing titanium-based reagents (Ti^0 or Ti^{II}), formed by reduction of $TiCl_3$ or $TiCl_4$ with different metals or metal salts, have been developed.[1-4d]

Among these, diastereoselective *dl*-pinacolization of aromatic aldehydes has been only found with systems derived from $TiCl_4/(i\text{-Bu})_2Te$ in DME,[6] $TiCl_4$/BuLi in Et_2O at -50°C,[7] and Cp_2TiCl_2/s-BuMgCl in THF at -78°C.[8] A titanium species obtained by reduction of Cp_2TiCl_2 with SmI_2, Zn, or *i*-Pr-MgI,[8] produces lower *dl*-selectivity.

We report here on the first $TiCl_3$-promoted reductive coupling of aromatic aldehydes in anhydrous solvent[9] at room temperature. By the choice of an appropriate solvent, *$TiCl_3$ does reduce benzaldehyde* and other activated aromatic aldehydes to the corresponding pinacols in good yields and, what is more important, the coupling is *dl*-stereodirecting.

Our method is exceedingly easier and more convenient compared with the ones so far reported:[6-8] the very high stereoselectivity obtained goes with the extremely simple experimental conditions. In addition the reducing solution of $TiCl_3$ in THF/CH_2Cl_2 (1:2) is commercially available[10] and stable for long periods, provided air and moisture are excluded.

The optimized procedure is as follows: a commercially available $TiCl_3$ solution (5 mmol) was added at once to a solution of the aromatic aldehyde (5 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 at room temperature.[11]

After 30 min. of stirring, the solution was quenched with H_2O (10 mL)[12] and extracted with ethyl acetate. Removal of the solvent *in vacuo* left the crude reaction products as a white solid, which was immediately subjected to a flash column chromatography separation to remove the unreacted aldehyde.[13] Isolated yields, *dl* and *meso* ratios, and melting points of the diols obtained are collected in the Table.

Under the mild conditions used, no by-products were formed and cyano, carboxy, and halide groups were tolerated in sharp contrast with the relatively low chemoselectivity shown by most titanium-based reagents.

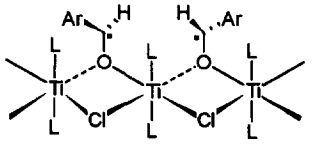
Aromatic aldehydes bearing an electron-donating group showed lower reactivity: for example, *p*-tolylaldehyde afforded the corresponding *dl*-diol in 35% yield only (entry 2) and no significant conversion (less than 10%) was observed with *p*-anisaldehyde.

In boiling CH_2Cl_2 for 30 min., the reactivity increased but, due to an *in situ* condensation of the diol with the unreacted aldehyde, the corresponding *dl*-2,4,5-triaryl-1,3-dioxolane was formed during the reaction (entries 1a and 2a).

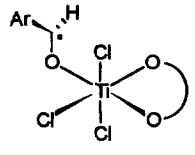
Although the relative ease of pinacolization is primarily determined by the reduction potential of the carbonyl group involved, the carbonyl-Lewis acid complexation increases the reactivity of the aldehyde[14]: in fact, when the reduction of benzaldehyde was performed in a coordinating solvent, such as THF (entry 1b), or in the presence of a strong basic ligand, such as pyridine (entry 1c), the Lewis acidity and coordinating power of the metal ion decreases, and the yields of *dl*-hydrobenzoin are lower than in CH_2Cl_2, a non coordinating solvent (entry 1).

The high preference for *dl*-diol formation may be explained by a Ti(IV)-bridging control[9] through a Ti(IV)-ketyl aggregate, like **A** or similar intermediate, in which the Ar groups are arranged *anti* to each other to minimize the steric interaction and the Ti(IV) Lewis acid reaches the stable octahedral arrangement with bridging ligands.[15]

When dimethyltartrate was used, as an additive (2.5 mmol), the *dl*/*meso* ratio dropped to 6.5 (entry 1d). Formation of a monomeric Ti(IV)-ketyl five-membered chelate complex, like **B** or similar, with the bidentate ligand[15] may saturate the octahedral coordinative valence of the metal ion and stabilization by aggregation may not be so important at the time of coupling. Consequently, steric control[9] may intervene prior to dimerization, thus affording the *meso* isomer.



A L= THF, Py, Cl



B

Due to the high *dl* stereoselectivity observed, enantioselective coupling reactions can be particularly envisaged.[16] Further studies dealing with this working hypothesis are in progress.

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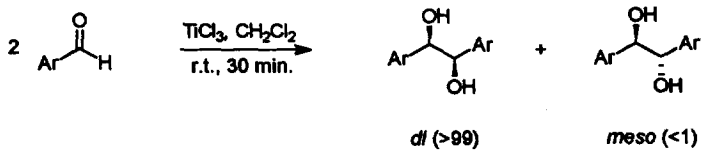
Table *dl*-Stereoselective Pinacolization of Aromatic Aldehydes Mediated by $TiCl_3/CH_2Cl_2$



Entry	Ar	Yield (%)[a]	*dl*/ *meso*[b]	mp (°C)	Lit. (°C)[c]
1	Ph	65	200:1	121	(121-2)[d]
1a[e]	"	70 (12)[f]	90:1		
1b[g]	"	41	100:0		
1c[h]	"	46	196:1		
1d[i]	"	64	6.5:1		
2	*p*-CH_3	35	>100:1	163	(163)[j]
2a[e]	"	43 (18)[f]	>100:1		
3	*p*-Cl	90	>100:1	156-7	(157)[m]
4	*p*-Br	96	>100:1	176	(-)[n]
5	*p*-CN	95	>100:1	232	(-)[o]
6	*p*-CO_2H	90	>100:1	312-4	

[a]Pinacol isolated yield. [b]Ratio determined by ^1H NMR (250 MHz) analysis of the crude reaction mixture.[17] [c]Melting point of *dl* isomer. [d]Ref. 2d. [e]Refluxing for 30 min. [f]Yield in brackets refers to 1,3-dioxolane. [g]THF (5 mL) was used as a solvent. [h]Pyridine (3.7 mmol) was used as an additive. [i](+)Dimethyltartrate (2.5 mmol) was used as an additive. [j]Collet, A. *Synthesis*, 1973, 664. [m]Ref. 7. [n]mp of *meso* isomer 137-8 °C: Gilmore, J. R.; Heaton, P. C. *J. Org. Chem.* 1973, *38*, 763. [o]mp of *dl-meso* mixture 201-3 °C: ref. 4d.

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9. In aqueous solution, the reducing power of Ti(III) redox-system is strongly pH dependent and hydrodimerization of benzaldehyde occurs only in strong basic media but, owing to the low coordination power of Ti(IV) under these conditions, diastereoselectivity is very poor (*dl/meso* ratio: 1.3): a) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1982**, *23*, 3517; b) Clerici, A; Porta, O. *J.Org. Chem.* **1985**, *50*, 76.

10. Available from Aldrich.

11. The change of colour observed during the reaction depends upon the nature of the aryl substituent.

12. At this stage, the *dl*-diols of *p*-CN, *p*-Br and *p*-CO_2H benzaldehydes precipitate directly from the reaction mixture and may be filtered off. However, to determine the *dl/meso* ratio the crude reaction mixture was extracted with ethyl acetate and the crude residue was analyzed by ^1H NMR prior to any further manipulation.

13. On standing, the *dl*-diol condenses with the unreacted aldehyde affording the corresponding *dl*-2,4,5-triaryl-1,3-dioxolane: see also ref. 6.

14. Ti(III) and TI(IV) furnish well defined 1:1 and 1:2 oxygen-donor complexes with benzaldehyde, respectively. a) Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet: Chem.* **1973**, *50*, 145; b) Pellissier, H.; Toupet, L.; Santelli, M. *J. Org. Chem.* **1994**, *59*, 1709.

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16. The reduction of benzaldehyde in the presence of (+)dimethyltartrate (entry 1d) is slightly enantioselective (4% opt. yield of (-)hydrobenzoin).

17. The *dl/meso* ratio of entries 1a-d was determined by comparing the ^1H NMR spectra of the crude reaction mixture with that of an authentic mixture of *dl* and *meso* isomers. The *dl/meso* ratio of entries 2-6 is less accurate since we tentatively assigned the very small signal at *ca* 0.1-0.2 ppm lower field to the *meso* isomer (see ref. 8).

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